Interactions within the social brain: Co-activation and connectivity among networks enabling empathy and Theory of Mind

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ABSTRACT

Empathy and Theory of Mind (ToM) have classically been studied as separate social functions, however, recent advances demonstrate the need to investigate the two in interaction: naturalistic settings often blur the distinction of affect and cognition and demand the simultaneous processing of such different stimulus dimensions. Here, we investigate how empathy and ToM related brain networks interact in contexts wherein multiple cognitive and affective demands must be processed simultaneously. Building on the findings of a recent meta-analysis and hierarchical clustering analysis, we perform meta-analytic connectivity modeling to determine patterns of task-context specific network changes. We analyze 140 studies including classical empathy and ToM tasks, as well as complex social tasks. For studies at the intersection of empathy and ToM, neural co-activation patterns included areas typically associated with both empathy and ToM. Network integration is discussed as a means of combining mechanisms across unique behavioral domains. Such integration may enable adaptive behavior in complex, naturalistic social settings that require simultaneous processing of a multitude of different affective and cognitive information.

1. Introduction

Successfully navigating everyday social interactions requires the ability to flexibly adapt to constantly changing environmental demands. This ability is greatly benefitted by an understanding of others' overt behaviors, but also of the motives underlying their behavior, that is, others' affective and cognitive states. Over the past 20 years of neuroimaging research, processes enabling us to smoothly navigate these social encounters have been extensively studied and gained more and more popularity. Especially the constructs of empathy and Theory of Mind (ToM) have attracted attention as key processes enabling social interactions. Empathy describes an affective representation of others' emotions (Gallese, 2003; Titchener, 1909), that is, the ability to share others' emotional states, while being aware that others are the source of those emotions (de Vignemont and Singer, 2006). ToM, on the other hand, describes a cognitive representation of others' mental states (Adolphs, 2009; Kanske, 2018), reasoning about and inferring others' thoughts, beliefs, or emotions (Frith and Frith, 2005; Mitchell et al.,

2005; Premack and Woodruff, 1978).

Classically, empathy and ToM have been regarded and investigated as isolated processes (Stietz et al., 2019). Empathy and ToM have been described as the "affective and cognitive routes" to understanding others (Kanske, 2018), referring to the fact that empathy enables the sharing of another's affective state through an isomorphic representation of their emotional state within oneself, while ToM describes the capacity to understand, make inferences about, and represent another's intentions, goals, or motives (Stietz et al., 2019). However, it is reasonable to assume that in naturalistic and real-life social interactions, this distinction is not as clear cut as it is in the context of a well-designed and controlled experiment. In everyday social interaction, one is presented with a plethora of different social information that must be processed and integrated in order to respond appropriately. It has been shown, for example, that ToM performance is impaired in situations where participants are confronted with highly emotional negative information (Kanske et al., 2016), pointing to a prioritization of empathy-processing in that context.

At the neural level, empathy and ToM are commonly associated with two distinct brain networks. Areas associated with ToM fall into bilateral temporo-parietal and anterior temporal cortex, medial prefrontal cortex, posterior cingulate cortex (PCC), and precuneus (Amodio and Frith, 2006; Frith and Frith, 2006; Mitchell, 2009; Schurz et al., 2014), areas largely overlapping with the so-called Default Mode Network (DMN, see Raichle et al., 2001; for an overlap of social affect and cognition networks with canonical resting-state network parcellations, see Schurz et al., 2020). The DMN is assumed to mediate self-generated cognition which is decoupled from the physical world (Andrews-Hanna et al., 2014), a necessary function for a wide range of ToM tasks (Buckner and Carroll, 2007; Bzdok et al., 2013; Frith and Frith, 2003; Lieberman, 2006; Mars et al., 2012a). As for empathy, activation is typically observed in bilateral anterior insular cortex, inferior frontal gyri (IFG), midcingulate cortex, supramarginal gyrus, as well as somatosensory cortex (Bzdok et al., 2012; Decety and Jackson, 2004; Kanske et al., 2015; Lamm et al., 2011). Empathy-associated networks show the highest overlap with the Ventral Attention (VAN) or Salience Network (Menon and Uddin, 2010; Schurz et al., 2020; Yeo et al., 2011), which has been associated with detecting behaviorally salient stimuli and directing neural resources towards their processing. It should be noted, however, that there is no one-to-one mapping of empathy-related neural activity to the VAN, and depending on the type of task employed, a range of other networks are engaged as well, such as the observation-action (mirror) system (see e.g., Oliver et al., 2018; Shamay-Tsoory, 2011; Timmers et al., 2018). As we observed highest overlap of empathy-related neural activity across a range of empathy studies with the VAN, we will focus our discussion here on this network. Using prototypical tasks, empathy and ToM have been shown to be unrelated, both at the behavioral and task-related neural level (Dziobek et al., 2006; Kanske et al., 2015; Rice et al., 2016; Shamay-Tsoory et al., 2009; Shamay-Tsoory and Aharon-Peretz, 2007): Kanske and colleagues (2016), for example, used Principal Component Analysis to show that behavioral measures and task-related neural activation of empathy and ToM are organized into clearly distinguishable, uncorrelated composites. This separability holds true not only in terms of social task-related behavioral measures and neural activity, but also for other, non-social task contexts and in terms of task-free brain organization. Networks associated with empathy (VAN) and ToM (DMN) have been found to be unrelated (Alcalá-López et al., 2018) and even anti-correlated in certain task-contexts and during rest (Bzdok et al., 2013; Chai et al., 2012; Fox et al., 2005; Trautwein et al., 2016; Zhou et al., 2018).

In contrast to this notion of independence, there is a considerable number of social affect and cognition studies yielding neural activation patterns that overlap with both, networks related to empathy and ToM, such as the VAN and DMN (for a review, see Schurz et al., 2020). For example, as part of a meta-analysis on neural networks of empathy for pain, Lamm and colleagues (2011) found not only engagement of the typical empathy network, but also of brain regions involved in ToM. The precuneus, ventral medial prefrontal cortex, medial and superior temporal gyrus, temporo-parietal junction (TPJ), and temporal pole were activated in a sub-set of studies wherein participants had to infer upcoming nociceptive stimulation from simple cues, rather than being shown the painful stimulation directly.

To further explore the relationship between empathy and ToM, we took an approach that went beyond a simple "semantic differentiation" between empathy and ToM and used a data-driven approach to distinguish between both constructs (Schurz et al., 2021). We identified 11 types of social tasks from the neuroscientific literature on empathy and ToM, covering a wide range of different stimuli and instructions. We then performed a meta-analysis and subsequent hierarchical clustering analysis (Schurz et al., 2021) to address the separability of these functions at the task- and overarching process-level. Interestingly, next to the two well-known and clearly separable empathy and ToM related networks described above, we also observed task-related neural activation falling into a third category. This category comprised tasks that contained both, affective and cognitive stimulus elements (e.g., reasoning about a character's next actions based on their emotions, see Kim et al., 2010; Sebastian et al., 2012; Völlm et al., 2006). At the neural level, activations associated with these tasks fell in areas typically associated with both empathy and ToM (Schurz et al., 2021).

Our previous meta-analysis has identified studies that concurrently engaged empathy and ToM networks (termed the "intermediate cluster"). However, our findings were based on averaging of activation patterns across different studies and not on measuring co-activation among areas. That is, the meta-analysis might yield conjoint activation of empathy and ToM areas when averaging across multiple studies, that may, however, not reflect systematic co-activation of these regions in individual studies. While the results of our previous meta-analysis yielded a comprehensive hierarchical model of how social affect and cognition is organized in the brain, questions regarding the nature of this neural organization remain unanswered: does the concurrent activation of regions associated with empathy and ToM in the intermediate cluster actually reflect cross-network interaction or mere averaging of activation from different studies, but no actual network interaction *within* these studies? And if we do observe true cross-network interaction in the intermediate cluster: how do these networks interact and what probes cross-network interactions? To address these issues, we here use meta-analytic connectivity modeling (MACM, Robinson et al., 2009; see also Friston, 1994; Koski and Paus, 2000) to estimate how empathy and ToM networks are functionally coupled, using the studies included in our previous meta-analysis (Schurz et al., 2021). Co-activation maps as identified using MACM correspond well with functional networks identified using resting-state functional connectivity (Kerestes et al., 2017; Robinson et al., 2012, 2009) and can be seen as a measure of functional coupling of different regions. During cognitive tasks, both MACM (Van Overwalle et al., 2015) and functional connectivity mapping (Krienen et al., 2014; Smith et al., 2016) show that functional networks systematically differ depending on the cognitive state elicited by stimuli and instructions.

Our previous meta-analysis of social affect and cognition tasks allowed us to characterize the hierarchical organization of how social affect and cognition are organized in terms of their neural representation. While we observed an interesting pattern of apparent cross-network interaction for complex social tasks (intermediate cluster), our previous analysis did not allow for a thorough characterization of these observed network interaction patterns. Here, we aim to investigate differing patterns of co-activation in social affect and cognition tasks to address our overarching question of the nature of context-dependent social network interaction. Using MACM, we want to probe situation-specific neural network configuration for tasks in which classical empathy and ToM networks are conjointly activated, integrating both processes: How do empathy and ToM networks interact in tasks that require conjoint processing of affective and cognitive information? We follow up on previously observed co-activation patterns (Schurz et al., 2021) by first identifying common regions of activation across all sub-domains of social affect and cognition. We then identify studies that show activation at the corresponding region of interest (ROI) and perform MACM on these studies. Lastly, we compare observed co-activation patterns with other meta-analytical and functional connectivity patterns.

2. Methods

We employed a modified version of MACM (see Robinson et al., 2009) similar to Van Overwalle, D'aes, and Mariën (2015) to determine patterns of co-activation across social affect and cognition dimensions. More precisely, in order to investigate specific patterns of co-activation within the realm of empathy and ToM paradigms, we used the assorted task groups from our previous meta-analysis (Schurz et al., 2021) as input into a MACM analysis. In the following, we will describe the study selection and clustering of social affect and cognition tasks that is based

on our previous meta-analysis, the methods of ROI selection, implementation of MACM as well as additional analyses to further characterize the co-activation patterns. Fig. 1 gives a detailed overview of the steps of analysis that were performed.

2.1. Hierarchical model of social cognition: a meta-analysis and hierarchical clustering

As the current study is based on the sample and clustering approach from our previous meta-analysis (Schurz et al., 2021), we will briefly describe methods relevant to this study here.

2.1.1. Literature search

For a complete description of search strategy and inclusion criteria, we refer the interested reader to our previous meta-analysis (Schurz et al., 2021). In short, we performed literature searches in common databases (PubMed, ISI Web of Science core collection) and included literature published up until November 2019. We identified studies using a combination of the following search terms: *neuroimaging* or *fmri* or *PET* AND *empathy* or *empathetic* or *altruism* or *sympathy* or *emotional contagion* or *compassion* (to represent studies in a broad empathy category) as well as *neuroimaging* or *fmri* or *PET* AND *theory of mind* or *mentalizing* or *mindreading* (to represent studies in a broad ToM category). Additionally, studies fulfilled selection criteria as required for coordinate-based meta-analysis (see e.g., Radua et al., 2012): reported coordinates had to correspond to standard space (MNI or Talairach), stem from whole-brain analysis, and use a consistent threshold throughout the entire brain. Only data from non-clinical, adult samples were included. Using these criteria, we obtained 188 studies (85 from

the empathy literature, 103 from the ToM literature, see also Fig. 1a) across 11 narrower task categories within the respective fields of research (for an overview of included task groups, see Schurz et al., 2021, or supplementary Tables S2 and S3).

2.1.2. Meta-analysis method and hierarchical clustering

For a detailed description of meta-analysis method and method of hierarchical clustering, we refer the reader to our previous meta-analysis (Schurz et al., 2021). In short, we performed effect-size based meta-analysis across 188 studies and 11 more narrow task-groups to receive task-group specific activation maps (see Fig. 1b). We then applied agglomerative hierarchical clustering to the assorted task-group activation maps to identify a hierarchical structure of social affect and cognition task groups (Fig. 1c). While multiple levels of clustering solutions were compared (e.g., one cluster representing all studies within the database), the optimal solution regarding our concepts of interest was found at a three-cluster level. These represented a) classical ToM tasks ("cognitive" task cluster, comprising False Belief, Trait Judgment, Strategic Games), b) classical empathy tasks ("affective" task cluster, comprising Observing Pain, Observing Emotions, Sharing Emotions or Pain, Reading the Mind in the Eyes), and c) tasks presenting affective and cognitive stimulus elements together ("intermediate" task cluster, comprising Evaluating Situated Emotions, Reasoning about Emotions, Rational Actions, Social Animations). Our initial database contained 57 studies from the cognitive, 58 studies from the intermediate, and 73 studies from the affective cluster.
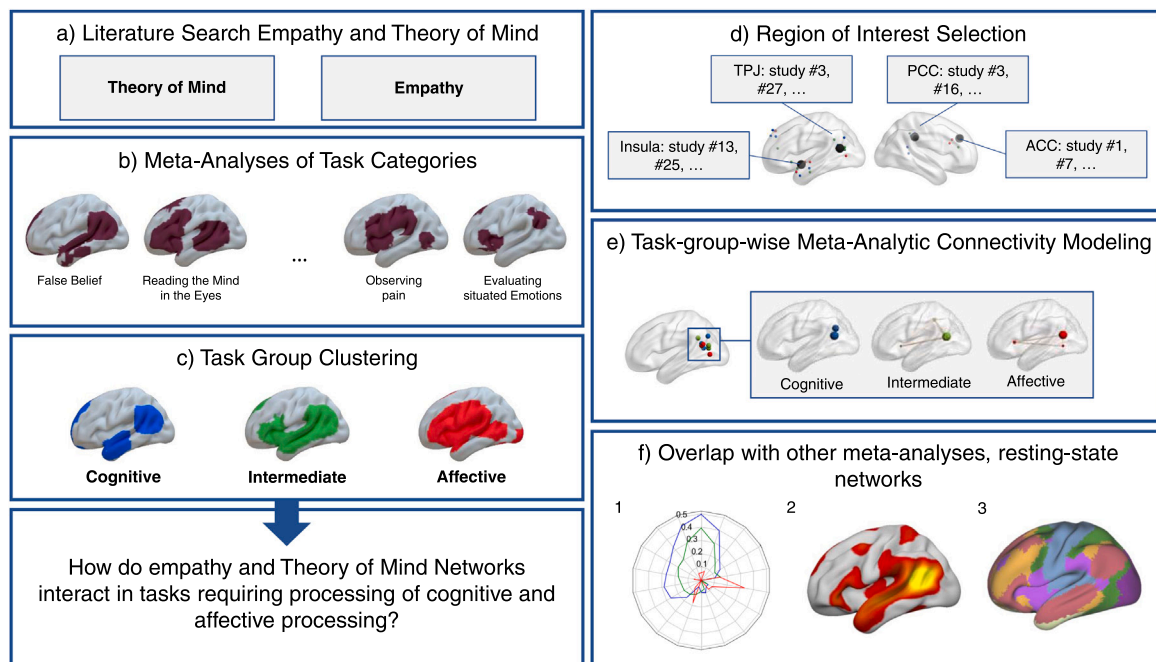
Fig. 1. Analysis workflow. (a) In the task-group wise meta-analysis and hierarchical clustering, we identified 188 studies (103 Theory of Mind, 85 Empathy) to be included in the meta-analysis. (b) Meta-analysis across 11 task groups revealed distinct associated neural patterns, (c) best described by a hierarchical three cluster solution, comprising classical Theory of Mind tasks (cognitive), classical empathy tasks (affective), complex social tasks, that present affective and cognitive information in concert (intermediate). To identify how empathy and Theory of Mind networks interact during combined affective and cognitive information processing, we performed meta-analytic connectivity modeling (MACM) on selected studies from our extended meta-analytic sample (initial meta-analytic sample as used in Schurz et al., 2021, extended literature search to include studies up until 2022. This yielded a sample of 206 studies, 99 from the empathy literature and 107 from the ToM literature). (d) We identified ROIs for the MACM analysis that showed activation across all tasks groups, allowing for a fine-grained differentiation between them in the course of the analysis, namely anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), temporo-parietal junction (TPJ), and insula. (e) For each ROI, we determined studies within our sample that showed activation at the corresponding ROI and performed meta-analytic linear contrasts to determine activation patterns specific to each of the three overarching task group clusters (cognitive, affective, intermediate). (f) Finally, we compared the task-group wise activation patterns with other meta-analysis maps (using Neurosynth decoding), and determined their overlap with basic networks of the brain (Yeo et al., 2011), as well as task-free functional connectivity profiles of the corresponding ROI.

2.2. Update of literature database

Additionally to the literature that was used in the previously described meta-analysis and hierarchical clustering analysis, we updated our literature database to also include studies published up until June 2022, in order to represent an up-to-date picture of the social affect and cognition literature. Therefore, we repeated the literature search to identify studies using the search terms described in Section 2.1.1 ("Literature search") limited to the time frame of November 2019 – June 2022. Using the screening method and applying the inclusion and exclusion criteria described above, we identified 14 additional studies from the empathy literature and 4 studies from the ToM literature, yielding a total sample of 206 studies (99 from the empathy literature, 107 from the ToM literature). Our final database contained 61 studies from the cognitive, 62 studies from the intermediate, and 83 studies from the affective cluster.

We base our analysis on the sample obtained from the literature search described above and will retain the three-group clustering of studies to describe neural activation patterns associated with classical empathy and ToM tasks, as well as tasks presenting elements from both empathy and ToM subfields.

2.3. Meta-analysis method, region of interest definition, and study selection

Arguably, ROI definition is the most important parameter to be set in any MACM analysis. In order to compare co-activation patterns between social affect and cognition task clusters, our ROIs should correspond to areas that show activation across all three task clusters. To identify areas that fulfill this criterion, we investigated common peaks of activation from the one-cluster solution in our agglomerative hierarchical clustering solution in the previous meta-analysis (Schurz et al., 2021).

To identify ROIs to be included in the further MACM analysis (Fig. 1d), activation peaks from our cross-task meta-analysis must fulfill the following additional criteria: they must ensure sufficient sample size to perform robust meta-analysis on and determine linear contrasts between task clusters (i.e., enough studies from each task cluster must show activation at the corresponding ROI, see e.g., Eickhoff et al., 2016), the ROI should lie within a network associated with social affect and cognition processes (to reduce the influence from processes secondary to our main research question, such as processing of visual or somatosensory information, see e.g., Schurz et al., 2020). Activation peaks were selected as ROIs for further analysis for which i) the ROI is located within a canonical neural network related to social affect and cognition processes (i.e., VAN, Frontoparietal Network, FPN, and DMN, see Schurz et al., 2020), and ii) at least 10 studies from the initial study database within each of the three task clusters show activation at the corresponding ROI (note that it is suggested to include at least 20 experiments in a meta-analysis to obtain results of moderate effect size, see Eickhoff et al., 2016. For reasons of feasibility, we here decided on a more liberal sample size threshold for our ROI selection but remain cautious to draw conclusion from analyses wherein less than 20 experiments per comparison group are included). To identify studies in our database that showed activation at the corresponding activation peaks, we calculated Euclidean distance from each reported coordinate from within our study database to each activation peak. Studies were deemed to show activation at the corresponding activation peak where Euclidean distance was smaller than 20 mm.

In a final step, we then performed a meta-analysis across the studies we identified in the previous step for each ROI (Fig. 1e). We carried out effect-size based meta-analyses using the anisotropic effect-size based algorithm of the seed-based *d* mapping method (AES-SDM 5.15, Radua et al., 2012, www.sdmproject.com, formerly Signed Differential Mapping). In contrast to other widely used meta-analysis methods such as Activation-Likelihood Estimation (Eickhoff et al., 2016), SDM incorporates the effect sizes of reported activations into the analysis,

allowing for a detailed description of the reported activation peaks from the literature. Based on studies' t-values and reported sample sizes, effect size and variance maps are created for each study (Hedge's *g* effect size measure, variance maps derived from reported effect size distribution). Statistical significance is determined by permutation tests randomizing the location of the voxels within a grey-matter mask (100 randomizations were performed). Results are reported in MNI space at a statistical threshold of $p < 0.005$ uncorrected (voxel-level) and at a cluster threshold of 10 voxels, which has been found to optimally balance specificity and sensitivity equivalent to a corrected threshold of $p < 0.05$ in the original studies (Radua et al., 2012). To determine differences in co-activation patterns between our three task clusters, we calculated contrasts using SDM's linear model function, which calculates the difference in effect size between meta-analyses while accounting for differences in sample size as well as within- and between-study variability.

2.4. Analysis of overlap with resting-state functional connectivity atlas and other meta-analyses

MACM approximates functional connectivity by looking at patterns of co-activation commonly observed for a specific ROI or set of ROIs (Robinson et al., 2009). Please note, however, that reported clusters of activation represent regions that are commonly observed to be activated in conjunction. We cannot, however, infer the underlying neuronal functional relationship between two areas, but rather infer functional relationship from common patterns of co-activations.

Analogous to Yang et al. (2015), we furthermore compared our co-activation maps to maps of functional magnetic resonance imaging (fMRI) resting-state functional connectivity (Fig. 1 f), as these provide ample information about the functional relationship between two spatially isolated neural regions (Cole et al., 2016; Passingham et al., 2002; Smith et al., 2009; Tavor et al., 2016). We obtained resting-state functional connectivity maps for each ROI as seed regions in a sample of 1000 subjects (for details of data collection, acquisition parameters, data preprocessing, and connectivity analysis, see Buckner et al., 2011; Choi et al., 2012; Yeo et al., 2011). Maps were obtained from the Neurosynth location tool (Yarkoni et al., 2011). In order to determine common activations between meta-analytic co-activation patterns, networks from a resting-state functional connectivity parcellation (Yeo et al., 2011), and corresponding patterns of fMRI seed-based functional connectivity, we used conjunction minimum analysis (see e.g., Nichols et al., 2005) as implemented in the image calculator utility of SPM 12 (www.fil.ion.ucl. ac.uk). We characterized overlaps in terms of percentage-wise overlap using a variant of the dice score: for each result map, we calculated the percentage of voxels that fell within different canonical resting-state networks (or seed-based functional connectivity maps). As our main interest lay in the overlap with specific parts of the functional connectivity atlas (namely the VAN, FPN, and DMN), we restricted our analysis of overlap to these three networks.

We also compared our results with a set of automatically generated meta-analyses across a multitude of topics. This allowed us to discuss our results in the context of a wide range of processes (we restricted our analysis of overlap to social processes, as these are of particular interest to the present study). We used the decoding tool from the Neurosynth database (Yarkoni et al., 2011), accessed through the neuroimaging repository Neurovault.org (Gorgolewski et al., 2015). Here, we input un-thresholded co-activation maps per ROI and task group (cognitive, intermediate, affective). We display posterior probabilities of the decoding, which describe the similarity between our result maps and automatically generated meta-analyses for topics identified by text mining of literature databases (i.e., the probability of a term being reported when brain activation at a certain voxel is present). We also display only those topics with highest similarity (posterior probability). Furthermore, we discarded topics of little interest to this analysis (anatomical labels, such as *insula*), as well as language-related terms

(such as *word*, *sentence*, or *syntactic*).

3. Results

We investigated meta-analytic findings of social affect and cognition studies to identify ROIs commonly activated across a wide range of empathy and ToM tasks. We then performed MACM, in order to investigate patterns of network co-activation specific to sub-processes of social affect and cognition (more cognitive, more affective, or complex social tasks).

We expected simultaneous processing of affective and cognitive stimuli (intermediate cluster) to be reflected in increased levels of cross-network interactions of networks related to empathy and ToM processing, such as the VAN and DMN, and recruitment of core regions previously associated with both empathy *and* ToM processing (e.g., anterior insula, IFG, TPJ, medial prefrontal cortex). Individual processing of either affective (affective cluster) or cognitive stimulus elements (cognitive cluster) should be reflected in co-activation patterns within the respective previously found empathy and ToM networks. More precisely, for tasks from the affective cluster, we expect co-activation patterns to be mainly restricted to networks previously associated with classical empathy processing (e.g., Fan et al., 2011; Lamm et al., 2011), including the VAN, Visual and Dorsal Attention Network (DAN, see also Schurz et al., 2020), and core empathy-related regions to be co-activated (e.g., anterior insula, IFG, supramarginal gyrus, somatosensory cortex). For tasks from the cognitive cluster, we expect that co-activation patterns will primarily be confined to areas in the DMN (e.g., PCC, precuneus, TPJ), and patterns of cross-network interaction will be comparably low (cf. Schurz et al., 2020).

3.1. ROI selection and study inclusion

In the meta-analysis across all studies in the initial study database (188 studies, see Schurz et al., 2021), we identified three broad clusters of activation (see supplementary Table S1 for an overview of identified clusters and activation peaks). Using our criteria described above, we identified four ROIs as the basis of our following analysis, namely right anterior cingulate cortex (ACC, with coordinates in MNI space at 2, 36, 32), PCC (at 0, −36, 34), left TPJ (at −52, −60, 16), and left insula (at −46, 2, −10).

In total, 155 studies showed activation at our four ROIs, Table 1 gives an overview of how they are divided among the different ROIs and task groups. Note that, since most studies within our database reported multiple regions of activation, studies could be included in the analysis for more than one ROI (e.g., one study might report activation in a False

Table 1
number of studies included in MACM analysis per ROI and task group, including number of participants.

ROI	incl. studies	Participants	Cognitive	Intermediate	Affective
ACC	56	1627	25 studies (501 participants)	18 studies (662 participants)	14 studies (464 participants)
PCC	51	1456	18 studies (392 participants)	20 studies (707 participants)	13 studies (357 participants)
TPJ	100	2522	38 studies (799 participants)	42 studies (1271 participants)	20 studies (452 participants)
Insula	62	1442	12 studies (292 participants)	22 studies (506 participants)	28 studies (644 participants)

Note. ROI: region of interest, ACC: anterior cingulate cortex, PCC: posterior cingulate cortex, TPJ: temporoparietal junction, cognitive: cognitive social task group, intermediate: intermediate social task group, affective: affective social task group.

Belief task at the PCC *and* TPJ and would therefore be included in the meta-analyses for both our PCC and our TPJ ROI). Supplementary Tables S2 and S3 give an overview of all studies included in the overall meta-analysis, as well as which studies were included in the MACM analysis.

3.2. Task-group specific patterns of network re-configuration

The task-group specific patterns of co-activation are summarized in supplementary Table S4. For each of our ROIs, we observed task-group specific network re-configurations. ROI-specific patterns of network re-configuration are displayed in Fig. 2. For reasons of brevity, we will focus our discussion on the three most strongly co-activated regions per ROI and task-cluster in detail (the interested reader is referred to supplementary Table S4 for a more in-depth account of each ROI and task-group specific co-activation network), but still discuss overall patterns of network re-configurations.

3.2.1. Cognitive cluster

Across our samples, studies within the cognitive task cluster exhibited similar patterns of co-activation. For our four ROIs, we observed strongest co-activation patterns for areas within the DMN. And while for some ROIs we observed significant co-activations with areas from networks other than the DMN, these were only sparse (e.g., subcortical areas within the PCC co-activation maps, areas in the VAN within the TPJ co-activation map). All ROI co-activation maps from the cognitive task groups displayed largest overlap with the DMN (with 68.6%, 69.8%, 61.3%, and 82.4% of activation for the cognitive co-activation maps lying within the DMN, for ACC, PCC, TPJ, and insula, respectively; see Fig. 3a-c for a graphical display of overlap with Yeo parcellation).

Besides clusters of co-activation at or approximately at the ROI itself, we observed clusters of highest co-activation in the precuneus (for insula, we found coupling with the right precuneus; for the ACC, we observed coupling with the left precuneus), left middle temporal gyrus (within PCC and insula co-activation maps), angular gyrus (ACC, PCC, TPJ, and insula co-activation maps), and superior frontal gyrus (TPJ co-activation maps).
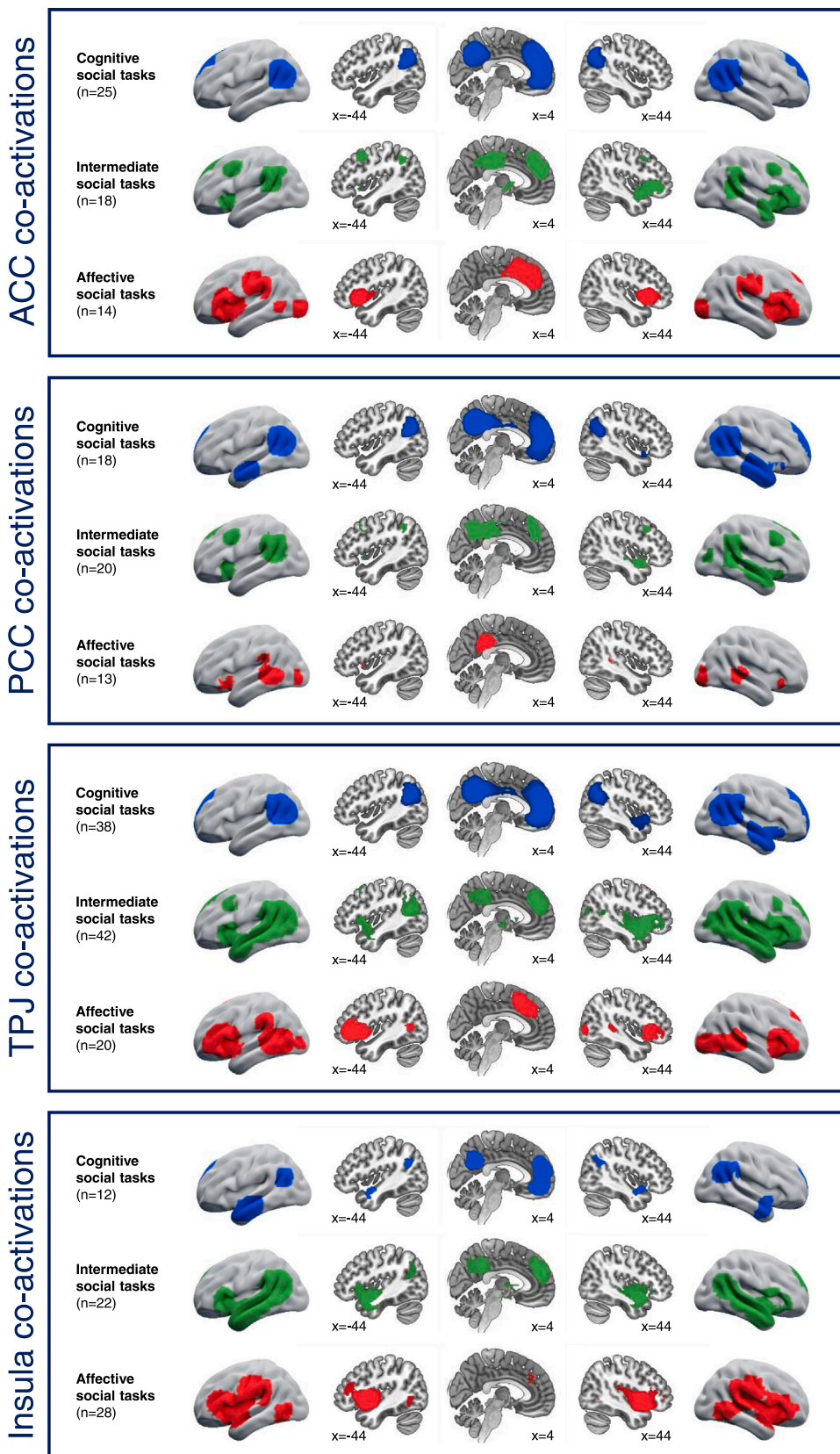
3.2.2. Affective cluster

In terms of co-activation patterns for studies from our affective task cluster, we expected to observe a similarly homogeneous picture. However, we found co-activation patterns to be somewhat more complex. Overall, the co-activation maps from the affective task cluster for the ACC, TPJ, and insula ROIs displayed largest overlap with the VAN (37.5%, 29.4%, and 32.9%), yet loadings on the FPN and DMN did not trail far behind. Interestingly, the co-activation map from the PCC ROI displayed a reversed picture, more similar to the patterns observed in the cognitive task clusters: Here, largest overlap for the co-activation map was observed in the DMN, FPN and VAN displayed similar loadings (see discussion section for possible explanation of this result pattern).

We observed clusters of strongest co-activation in the insula (left insula within the ACC and PCC co-activation maps, right insula within the ACC and TPJ co-activation maps), median cingulate gyrus (right median cingulate gyrus in the ACC co-activation map, left median cingulate in the PCC co-activation map), postcentral gyrus (right postcentral gyrus in the ACC co-activation map, left postcentral gyrus in the insula co-activation map), left supramarginal gyrus (ACC co-activation map), middle temporal gyrus (left middle temporal gyrus in ACC, PCC, TPJ and insula co-activation maps, right middle temporal gyrus in PCC co-activation map), and left IFG and pre supplementary motor area (TPJ co-activation maps).
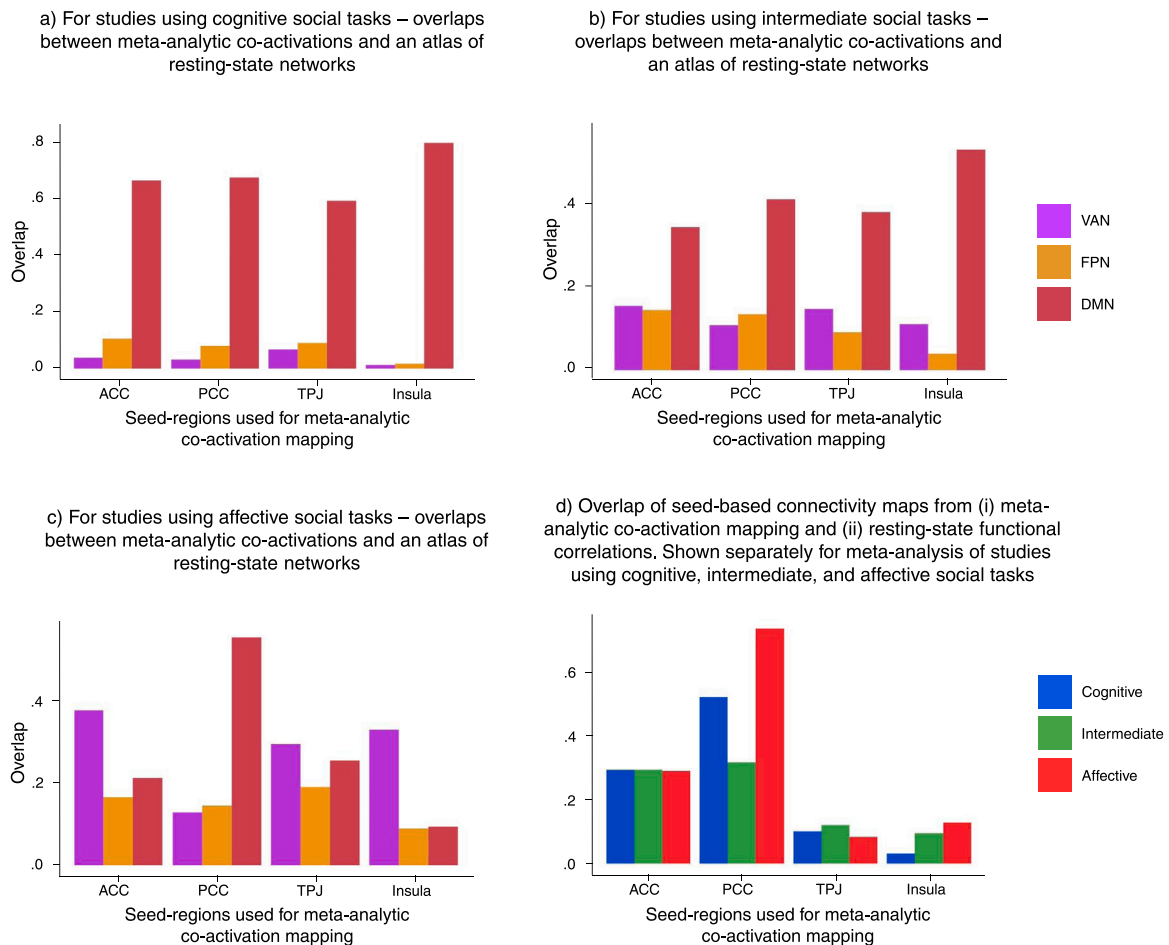
3.2.3. Intermediate cluster

As expected, patterns of co-activations for studies from the

Fig. 2. Task-group wise patterns of meta-analytic co-activation for each ROI. Linear contrasts between task-group clusters (cognitive cluster in blue, intermediate cluster in green, affective cluster in red) reveal patterns of network co-activation overlapping to some extent but showing clearly discernable differences between task groups. Results are portrayed for the anterior cingulate cortex ROI (box ACC co-activations, top), posterior cingulate cortex ROI (box PCC co-activations), temporo-parietal junction ROI (box TPJ co-activations), as well as the insula ROI (box Insula co-activations, bottom).

intermediate cluster showed the most heterogeneous picture. For all four ROIs, the co-activation maps from the intermediate task cluster showed activation clusters lying within most of the seven resting state networks (except for the Somatomotor Network), as well as within subcortical regions. For all four ROI co-activation maps, the majority of activation fell within the DMN (35.5%, 42.5%, 39.3%, and 54.9%, for ACC, PCC, TPJ, and insula, respectively), but we also observed considerable overlap with the VAN (16%, 11.2%, 12.2%, and 11.5%, for ACC, PCC, TPJ,

a) For studies using cognitive social tasks – overlaps between meta-analytic co-activations and an atlas of resting-state networks

b) For studies using intermediate social tasks – overlaps between meta-analytic co-activations and an atlas of resting-state networks

c) For studies using affective social tasks – overlaps between meta-analytic co-activations and an atlas of resting-state networks

d) Overlap of seed-based connectivity maps from (i) meta-analytic co-activation mapping and (ii) resting-state functional correlations. Shown separately for meta-analysis of studies using cognitive, intermediate, and affective social tasks

Fig. 3. Analysis of overlap of co-activation maps, canonical resting-state networks, and functional connectivity maps. (a-c) Overlap of task-group specific co-activation patterns with canonical resting-state networks associated with empathy and ToM, (d) as well as corresponding seed-based functional connectivity maps.

and insula, respectively). Note, though, that in contrast to co-activations from the cognitive cluster, overall overlap was considerably smaller, and overlap with other canonical resting-state networks was not negligible.

Clusters of highest co-activations were observed at the left middle temporal gyrus (TPJ and insula co-activation maps), superior frontal gyrus (left superior frontal gyrus in ACC and PCC co-activation maps, right superior frontal gyrus in the insula co-activation map), median cingulate gyrus (left median cingulate gyrus in the ACC and PCC co-activation maps, right median cingulate gyrus in the TPJ co-activation map), left supramarginal gyrus (ACC and PCC co-activation maps), right insula (anterior insula in the PCC co-activation map, insula in the TPJ co-activation map), right superior temporal gyrus (insula co-activation map) and right IFG (ACC co-activation map).

3.3. Analysis of overlap with resting-state functional connectivity

As we wanted to analyze the underlying neural functional relationship of our ROIs and their co-activation patterns, we compared co-activation maps with the respective seed-based functional connectivity maps of the ROIs. An interesting pattern emerged when looking at the overlap of co-activation and seed-based functional connectivity maps (see Fig. 3d). For ACC and PCC, a substantial amount of the co-activation map overlapped with the corresponding seed-based connectivity map (for ACC: overlap cognitive cluster 29.3%, intermediate cluster 29.4%, and affective cluster 28.9%; for PCC: for cognitive cluster 52.2%, for intermediate cluster 31.7%, and for affective cluster 73.6%). The opposite pattern was present for the overlap of TPJ and insula co-activation and corresponding seed-based connectivity maps: Here,

only a maximum of ~13% of a co-activation map overlapped with the corresponding functional connectivity map (for TPJ: cognitive cluster 10.2%, for intermediate cluster 12%; for affective cluster 8.3%; for insula: cognitive cluster 3.1%, intermediate cluster 9.6%, and affective cluster 12.8%). This points to a rather high level of network integration (that is to say, cross-network interaction); possible mechanisms and implications of these results will be explored in the discussion section.

3.4. Analysis of overlap with other meta-analyses

Finally, we used Neurosynth decoding to characterize patterns of co-activation in terms of associations with other meta-analysis maps. Fig. 4 shows the resulting decoding maps for our ROIs and each task group (for a list of most strongly associated decoding terms, see supplementary Table S10). Interestingly, resulting topics overlapped substantially for the cognitive and intermediate cluster, while the affective cluster displayed a more independent topic-profile. For the cognitive and intermediate cluster, decoding showed mostly ToM-related terms, such as "theory mind", "mentalizing", "social cognition", and "belief". Furthermore, a high posterior probability for the term "social" was also decoded for cognitive and intermediate co-activation maps, while this association was not as strong for the affective cluster co-activation maps. Additionally, for the cognitive cluster, terms such as "self-referential" or "intentions" showed high posterior probabilities (terms also associated with the DMN). Decoding for the affective cluster revealed terms such as "pain" or "painful", "valence", "emotional", as well as the clinical term "ptsd" (post-traumatic stress disorder). And while these terms were also decoded for the cognitive and intermediate cluster, their posterior
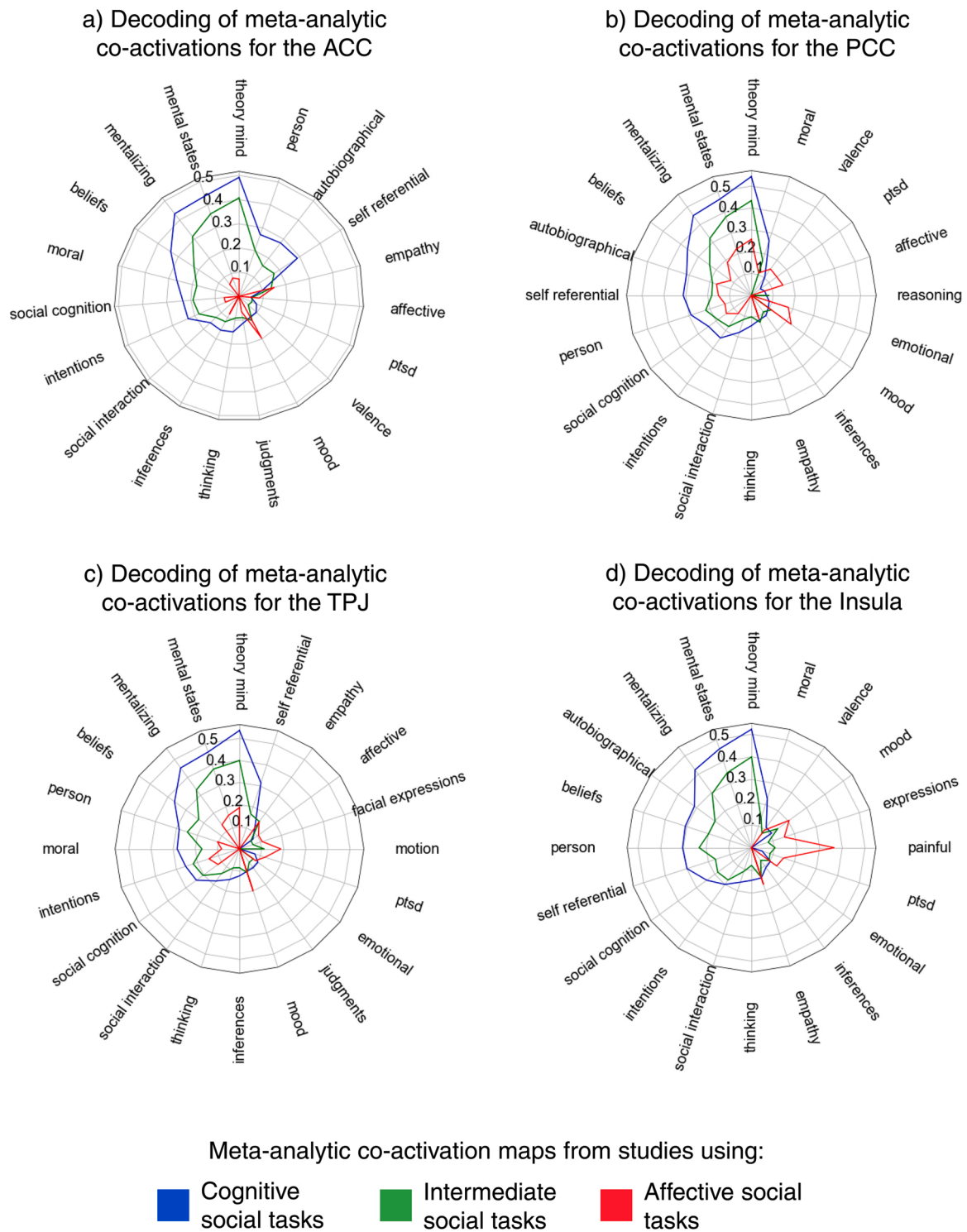
Fig. 4. Neurosynth decoding of task-group wise co-activation maps. Figures represent decoding of un-thresholded task-group wise linear contrast maps for ACC ROI (a), PCC ROI (b), TPJ ROI (c), and insula ROI (d). Displayed are posterior probabilities (pearson correlation coefficient) of terms associated with neural activation patterns. For illustrative purposes, we only included social terms (note that while ptsd is technically a clinical term, the diagnosis is linked to difficulties in relevant domains and was therefore portrayed as well), that were associated with more than one task group to allow comparison between groups. We discarded anatomical or other non-social/ cognitive terms, as these were not as relevant to our analysis.

probability for these terms was considerably lower. One term that showed similar posterior probabilities across task groups in most ROIs was the term "empathy". Interestingly, decoding maps did not differ substantially between ROIs in terms of which topics were decoded. Only their association (the posterior probability) differed between task clusters (for terms that were associated with cognitive and intermediate

cluster, most terms showed higher association with the cognitive cluster).

4. Discussion

In this meta-analysis, we investigated task-related patterns of cross-

network interactions and re-configurations in two domains of social cognition (empathy, ToM). We evaluated whether patterns of co-activation would change, depending on the different tasks employed to measure each domain. Furthermore, we compared resultant domain-specific patterns of co-activation with basic (resting-state) networks of the brain and other existing meta-analyses. Our main hypothesis was that while empathy and ToM represent independent processes, some task characteristics require conjoint activation of both networks.

Our previous analysis (Schurz et al., 2021) introduced a tripartite hierarchical model of social affect and cognition, including robust and data-driven evidence for co-activation of areas typically associated with empathy *and* ToM. This analysis did not, however, allow us to test whether the common activation of those networks arose from the simultaneous activation of both networks within one task, or whether an averaging of activation across multiple task-specific activation patterns drove these effects. This analysis was not designed to investigate the interaction between individual nodes of an overall activation cluster, but rather described the activation cluster as a whole. Furthermore, our method of analysis did not allow for us to investigate how the social context modulated the emerging patterns of co-activations. Nonetheless, these findings pose the question how social processing is implemented within the brain when socio-affective and -cognitive demands are simultaneously present. Here, we followed up on this finding and show that for tasks presenting affective and cognitive stimulus elements in combination (intermediate task cluster), empathy and ToM networks are indeed engaged simultaneously (e.g., Amodio and Frith, 2006; Bzdok et al., 2012; Fan et al., 2011; Frith and Frith, 2006; Lamm et al., 2011; Mitchell, 2009; Saxe and Kanwisher, 2003; Schurz et al., 2014).

More specifically, across our four social affect and cognition ROIs, strongest co-activations were observed in the left middle temporal gyrus, superior temporal gyrus, left median cingulate/ paracingulate gyrus, superior frontal gyrus, left supramarginal gyrus, as well as right insula and left IFG, areas previously associated with both empathy and ToM networks (Schurz et al., 2021). Our findings of cross-network interaction are in line with a considerable number of social affect and cognition studies that report neural activation patterns distributed among a range of different networks related to empathy and ToM, such as the DMN and VAN (for a review, see Schurz et al., 2020). Co-activation of both empathy and ToM networks has been associated with more naturalistic social cognition (e.g., Harvey et al., 2013; Hildebrandt et al., 2021; Kanske et al., 2015; Reyes-Aguilar et al., 2017; Tholen et al., 2020; Zaki et al., 2009) and everyday social interactions (e.g., Deuse et al., 2016; Schilbach et al., 2013, 2008; Wolf et al., 2010). It could be argued that cross-network interactions might represent one process enabling or inhibiting the other (in the sense that, e.g., sharing another's emotion might facilitate taking their perspective, in the case of positive coupling of empathy and ToM networks). In line with this notion, Kanske and colleagues (2016) observed inhibitory cross-network interaction from nodes of the FPN onto DMN, a pattern that became even more pronounced in highly emotional situations, which could represent processing of affective stimulus elements (i.e., empathizing with the demonstrator) being prioritized over processing of cognitive stimulus elements (i.e., mentalizing). They suggest that a down-regulation of the DMN might represent re-orienting of attentional resources towards salient aspects of a social situation that require the most immediate action (Menon and Uddin, 2010). On the other hand, positive coupling (excitatory influence from one network onto another) has been observed in response to increased task complexity (Shine et al., 2016) or when information from different sources must be integrated for successful task performance (see e.g., Schuwerk et al., 2017). A pattern of positive coupling between empathy and ToM networks is commonly seen, for example, in studies wherein participants must infer a character's beliefs or intentions based on linguistic information (Tettamanti et al., 2017; van Ackeren et al., 2016) or another's actions (Ciaramidaro et al., 2014; Schippers et al., 2009, 2010; Sperduti et al., 2014; Spunt and Lieberman, 2012a; Thioux et al., 2018). This example of informational integration

(e.g., participants must integrate information about another's actions in order to infer their mental state) is a potentially relevant process for multiple studies from our intermediate task group, and also a common pattern of co-activation that we observed for our intermediate task group. For example, the co-activation map for our insula ROI (located in the VAN) presents strong coupling with the superior temporal gyrus, superior frontal gyrus, middle temporal gyrus, and precuneus, areas located within the DMN. Similarly, for the TPJ ROI co-activation pattern (located in the DMN), we observed strong coupling with the right insula located in the FPN.

4.1. What are the task characteristics requiring cross-network interaction?

Our analysis of co-activation on the basis of activation peaks does not allow for a comparison of directed connectivity as is discussed above, however our results show that in tasks from the intermediate cluster especially, informational exchange between nodes of the DMN and the Control Networks (as VAN, FPN, and DAN are sometimes referred to, see Cole et al., 2014; Dosenbach et al., 2008) seems to be especially relevant. Rich, naturalistic social cognition and social interaction tasks (Schilbach et al., 2008; Zaki et al., 2009) require simultaneous processing of a multitude of different information, blocking out those that are irrelevant to the task at hand and integrating those functions that are required to be performed conjointly (see e.g., Anticevic et al., 2012; Goulden et al., 2014; Trautwein et al., 2016; Vatansever et al., 2015; Wen et al., 2013). Our tasks included in the intermediate task cluster paint a rather heterogeneous picture in terms of task characteristics. However, most tasks gave participants contextual information about the content of the task, portray social interactions (dynamically using videos, statically using written text) with human or abstract non-human demonstrators (e.g., a comic character, anthropomorphic geometric forms), and required participants to reason about and/or report their own or an observed other's state of mind (emotional, cognitive).

In contrast to classical ToM tasks, for example in tasks from the intermediate cluster, participants are presented with both cognitive and affective information simultaneously. Inference of mental states is supported by giving the participants information about the context of a social situation, for example through narrations. Similar to our results presented here, this intricate pattern of cross-network interactions between "social cognition networks" has been shown in studies wherein participants were asked to infer mental states from linguistic information (such as mutterings, Tettamanti et al., 2017; van Ackeren et al., 2016), from actions (Ciaramidaro et al., 2014; Spunt and Lieberman, 2012b; Thioux et al., 2018), or in socially-guided attentional reorienting (Schuwerk et al., 2017; for a comprehensive review of cross-network connectivity in the context of social affect and cognition, see also Schurz et al., 2020). This aspect of informational integration for tasks from the intermediate cluster is also very pronounced in the comparison of our results with other meta-analyses (Neurosynth decoding). The decoding patterns for co-activation maps from the intermediate and cognitive task group appear to be quite similar for the social terms, but the decoding patterns for non-social terms for the intermediate (and affective) task group were much more diverse than portrayed above. Next to anatomical, we also found a multitude of language-related or other non-social terms (e.g., "task", "monitoring" or "error", see supplementary Table S10). This points to the importance of an integration of different processes for tasks from the intermediate task group: while the decoding profile for classical ToM tasks is rather "clean cut" in that we primarily found terms related to mentalizing, the more complex social tasks seem to require a wider range of different processes to be engaged conjointly (Schilbach et al., 2013; Zaki et al., 2009).

4.2. Network integration paves the way for complex, naturalistic social cognition

The VAN and DMN are richly interconnected networks, portraying extensive brain-wide patterns of connectivity, and studies have shown that these can be flexibly updated to adapt to changing task demands (Ciaramidaro et al., 2014; Power et al., 2011; Sakai, 2008; Spunt and Lieberman, 2012b). Core nodes of the empathy and ToM networks, which we have so far largely equated with the VAN and DMN, are furthermore characterized by a high degree of connectivity to other regions. Therefore, a holistic model of, for instance, TPJ and insula functioning can benefit from considering how they are connected with the rest of the brain. While network organization is constrained by anatomical and functional connections (see e.g., Bullmore and Sporns, 2009; Honey et al., 2009), neural systems can flexibly reconfigure their structure to adapt to changing environmental or task demands (for a review, see Shine and Poldrack, 2018). Several studies found that network segregation, strong grouping of a network into its sub-components, showing high intra-network and low inter-network connectivity, is associated with more automatic processing (e.g., motor learning: Bassett et al., 2015; sustained vigilance: Sadaghiani et al., 2015). Network integration, on the other hand, that is, how modular networks interact among their sub-components, has been shown to be associated with tasks requiring more effortful and controlled processing, or in response to cognitively demanding tasks (e. g., memory recall: Fornito et al., 2012; Spreng et al., 2010; high-level n-back task and social animations: Shine et al., 2016).

For complex, naturalistic social cognition tasks, network integration as a means of integrating mechanisms across unique behavioral domains can potentially be a relevant mechanism for enabling complex social cognition (Shine and Poldrack, 2018). We observe high levels of network integration (in the sense of co-activation of different networks) especially for the intermediate cluster, but interestingly also for the affective cluster. While a large part of the different ROIs' co-activation maps for the intermediate cluster fall into the DMN, we also observed large overlap with other social cognition related networks, such as the VAN and the FPN. Interestingly, we furthermore observed considerable network integration for the co-activation patterns of our affective task cluster, pointing to a wider range of processes that enable classic empathic processing. Previously, we reviewed cross-network interactions for different classes of empathy tasks and found a similar pattern, namely that certain empathy tasks required interaction of different canonical brain networks (Schurz et al., 2020). Greater co-activation of visual and sensorimotor networks points to the relevance of lower-level sensory processing for some classical empathy tasks, while for tasks from the intermediate cluster, we observed more involvement of other higher cognitive and social-cognitive networks in addition to sensory networks.

Apart from simultaneous DMN and VAN activation as a measure of cross-network interaction, we can furthermore attempt to quantify levels of network integration and segregation in terms of overlap of co-activation patterns with seed-based functional connectivity patterns for the corresponding ROI. Here, large overlap would point to lower levels of network integration, while smaller overlap would point to higher levels of network integration (as the co-activation patterns in response to a certain task would represent patterns of activation that go beyond or are even opposite to how that region is connected at rest). We see largest overlap for ACC and PCC co-activation maps (cognitive: 29.3%, affective: 28.9%, intermediate: 29.4%; cognitive: 52.2%, affective: 73.6%, intermediate: 31.7%; respectively) and lowest for insula co-activation maps (cognitive: 3.1%, affective: 12.8%, intermediate: 9.6%). This could suggest that in the context of social cognition tasks, the TPJ and insula take over hub roles, where patterns of co-activation can flexibly re-configure across a wide range of other networks.

A considerable number of neural regions have been associated with the neural representation of empathy and ToM (Fan et al., 2011; Lamm

et al., 2011; Schurz et al., 2014; Timmers et al., 2018). In our own and other previous work, insula and TPJ have been found as key nodes of the social affect and cognition networks (Schurz et al., 2021), and have been preferentially linked to empathy and ToM, respectively (Kanske et al., 2015). Our results provide evidence that relativizes the notion of independent empathy and ToM networks: we show that certain task characteristics probe the interaction of empathy and ToM networks, namely tasks that simultaneously process affective and cognitive information. This is in line with previous findings showing that the interaction of empathy and ToM is crucially dependent on the specific context in which they are experienced. With more complex contextual demands placed on empathy and ToM processing, the separation of empathy and ToM becomes blurry (see e.g., Hillebrandt et al., 2014; Kanske et al., 2016; Schuwerk et al., 2014; Tettamanti et al., 2017), despite the processes being principally separable (as seen, for example, in selective impairments or developmental trajectories of empathy and ToM, see Reiter et al., 2017; Stietz et al., 2019; Winter et al., 2017).

Given their structural integration into whole-brain architecture, TPJ and insula lend themselves as key network hubs facilitating interaction between networks and functions necessary to complex social tasks. A plethora of work speaks to the heterogeneity of TPJ and insula functional profiles: they have been associated with processes such as empathy, ToM, self-other distinction, attention, and sensorimotor integration (Cauda et al., 2011; Decety and Lamm, 2007; Dosenbach et al., 2007; Jakobs et al., 2012; Menon and Uddin, 2010). In fact, functional connectivity, meta-analytic clustering, and MACM studies suggest a bipartite (e.g., Cauda et al., 2012; Krall et al., 2015; Numssen et al., 2021) or tripartite (e.g., Bzdok et al., 2013; Chang et al., 2013; Mars et al., 2012b) subdivision of functional clusters within the insula and TPJ, including diverse connectivity profiles for each cluster. For example, Chang et al. (2013) suggests a subdivision of the insula into a dorso-anterior, ventro-anterior, and posterior cluster based on a resting-state functional connectivity parcellation and large-scale meta-analysis. Based on the connectivity profiles associated with each insular cluster and specific functional profile associated with them, the authors name the insula as perfectly suited to be an integrational interface between feelings, cognition, and action. Furthermore, the (anterior) insula has been named an integral hub in mediating dynamic interactions between large-scale networks (Menon and Uddin, 2010; Power et al., 2013; Sridharan et al., 2008). The TPJ has mainly been associated with attentional and social cognitive processing, linking processing of internal and external information (Bzdok et al., 2013; Krall et al., 2015). However, connectivity profiles associated with a three-cluster subdivision arguably could suggest that TPJ may well be engaged in a wider range of processes (Mars et al., 2012b), and suggest a critical role in contextual integration (Jakobs et al., 2012). Taken together, it could be argued that insula and TPJ represent dynamic social affect and cognition hubs that, given how they are embedded in overall brain network architecture, are integral in facilitation of cross-network interaction in complex social tasks.

4.3. Limitations

In this meta-analysis, we investigated the nature of social cognition cross-network interactions, and the conditions that prompt these cross-network interactions. We should note, however, that our meta-analysis set-up left some limitations that might constrain the generalizability of our results. First, the data and ROI selection for our analysis might have introduced some bias into our analysis. Typically in a MACM analysis, widely available online neuroscience data-repositories such as Neurosynth or BrainMap are employed to identify studies that report activation at the corresponding ROI (see e.g., Robinson et al., 2012, 2009). However, since our focus lay on a narrowed field of study (social cognition), we decided to limit our database in this regard (see also Van Overwalle et al., 2015 for a similar approach). We furthermore decided to select our ROIs from within our database rather than select ROIs that

have been shown to be involved in different domains of social cognition (such as the superior temporal sulcus, see e.g., Alcalá-López et al., 2018; Deen et al., 2015). While it would also have presented advantages to select an "external" ROI, due to the focus of our study (we wanted to investigate network co-activation of empathy and ToM, exclusively) and for reasons of feasibility (ensuring sufficient sample size for further analysis), we decided on a data-driven approach for ROI selection. Note that we did, however, perform the same analysis with anatomically defined social cognition ROIs (namely bilateral TPJ and anterior insula), which yielded similar results to the ones reported here (see supplementary Tables S5 and S6 for an overview of included studies, S7 for results, and Section 3 of the supplementary material for an overview of additional analysis methods and included studies).

Furthermore, we must note the difference in sample sizes of our different sub-analyses. For reasons of feasibility, we decided to choose those ROIs for our analysis that showed activation in at least ten studies per task group, which yielded a somewhat un-balanced sample size both between ROIs and between task groups. However, we did find comparable results across ROIs and task-groups (especially with those subsets of analysis wherein the sample size is relatively balanced across task-groups, i.e., the TPJ) and therefore believe our results to be principally generalizable (see also results of jackknife sensitivity analysis in supplementary Table S8).

Finally, we would like to point out that, while we can assume functional connectivity from observed patterns of co-activation, we cannot make causal claims as to the nature of this relationship. Future studies might address these points using appropriate methods of analysis, as has already been done in several studies (see e.g., Kanske et al., 2016; Regenbogen et al., 2013; Schuwerk et al., 2017, 2014; Tettamanti et al., 2017).

5. Outlook

Humans are an inherently social species, and processes enabling us to successfully navigate through our social world are continually attracting more and more research interest. In the present meta-analysis, we summarize neuroimaging research relating to social affect and cognition from the past 20 years, putting a special focus on how these two functions jointly activate and interact in situations where both affective and cognitive information must be processed simultaneously. We perform meta-analytic connectivity modeling on a sample of 155 studies (including 3831 participants) and show an intricate and complex pattern of social domain-specific network re-configuration, and cross-network interactions for those social domains that present affective and cognitive stimulus elements in conjunction.

While co-activation patterns associated with classical empathy and ToM tasks resemble neural patterns previously termed empathy or ToM-networks (see e.g., Bzdok et al., 2012; Fan et al., 2011; Lamm et al., 2011; Schurz et al., 2021, 2014), co-activation patterns associated with our intermediate task cluster show activation in regions associated with both empathy and ToM. We discuss our findings in the context of brain network organization (Shine and Poldrack, 2018), and examine network integration as a mechanism required in complex, naturalistic social situations. Here, multiple sources of (affective and cognitive) information must be processed simultaneously in order to facilitate social interactions. Taken together, our findings highlight the importance of a holistic, integrative account of social information processing at the neural level to understand the full extent of how the social brain functions, a key question not only in the context of basic research, but also in applied contexts (e.g., clinical psychology: Lehmann et al., 2019).

Declaration of Competing Interest

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2023.105080.

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